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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,328	12/09/2004	Jeffrey A Smith	00789-05	7405

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UNIVERSITY OF VIRGINIA PATENT FOUNDATION
250 WEST MAIN STREET, SUITE 300
CHARLOTTESVILLE, VA 22902

EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	PAPER NUMBER
1623	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,328	SMITH ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-28,32 and 51-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-28,32 and 51-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/16/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A Request for Continued Examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed 3/5/2007 has been entered.

The Request for Continued Examination filed 3/5/2007 has been carefully considered. The following information provided in the amendment affects the instant application:

1. Claims 1-9, 29-31, 33-38 and 48-50 have been canceled.

2. New Claims 51-53 have been added.

3. Claims 21, 25 and 32 have been amended.

4. Claims 10-20 and 39-47 have been withdrawn.

5. Remarks drawn to objections to specification (abstract) and rejections under 35 USC 112, first and second paragraphs, 102 and 103 advanced in the previous office action.

Claims 21-28, 32 and 51-53 are currently under examination.

Specification

The objection to the abstract advanced in the previous office action has been overcome by filing of the abstract o a separate sheet.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-28 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for the treatment of prostate and breast cancer using the compound of formula (III) and antisense oligonucleotides and interfering oligonucleotides, does not reasonably provide enablement for the treatment of all other types of cancers using the compound of formula (III) and the treatment of cancers using any other Rsk specific inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

(A) The breadth of the claims
(B) The state of the prior art
(C) The level of one of ordinary skill
(D) The level of predictability in the art
(E) The existence of working examples
(F) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

Claim 21 is drawn to a method of treating cancer characterized by excessive Rsk activity comprising administration of a composition comprising a compound of formula III. Claim 25 is drawn to the same method comprising administering an Rsk specific inhibitor. The methods as

recited are seen to be treating all types of cancers/tumors with any Rsk specific inhibitor as broadly recited in claims 21 and 25.

The state of the prior art

The skilled artisan would view cancers as not treatable with one medicament or therapeutic regimen. Treatment efforts and efforts to cure all cancers have produced only isolated identifiable positive results. See *In re Application of Hozumi et al.*, 226 USPQ 353. Moreover, it is well known that so far no single chemotherapeutic agent has been found to be useful in the treatment of **all** cancers, or even useful in the treatment of all types of breast cancers; and colon cancers; and prostate cancers; and leukemias. For example, breast cancers and leukemia do not share a common cause and differ in their methods of treatment, i.e., breast cancers are routinely with estrogens, antiestrogens, and/or androgens, unlike leukemia which is routinely treated with I-asparaginase, daunorubicin, and purine analogs.

Level of One of Ordinary Skill in the Art

One of ordinary skill in the art would be a Physician with an M.D./PhD.

The level of predictability of the art

Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Moreover, it is known that repeated therapeutic failures, after promising in-vitro test results, suggest to the skilled artisan that claims based on in-vitro data, directed to treating cancer generally, are highly unpredictable, as taught in Trisha Gura's article in *Science*, November, 1997 (PTO-892):

"[T]he institute started by pulling together mouse models of three tumors: a leukemia, which affects blood cells; a sarcoma, which arise in bone, muscle, or connective tissue; and carcinoma, the most common cells and includes such major killers as breast, colon, and lung cancers. Initially, many of the agents tested in these models appeared to do well. However, most worked against blood cancers such as leukemia and lymphoma, as opposed to the more common solid tumors. And when tested in human cancer patients, most of these compounds failed to live up to their early promise." (emphasis added, see for example, the middle column of the article).

Based on the known teachings of the cancer treatment such as in Trisha Gura's reference, one of skill in the art would recognize that it is highly unpredictable in regard to the treatment in the instant case, including treating numerous and various tumors: gynacological tumors, ovarian carcinomas, testicle tumors, prostate carcinomas, skin cancer, kidney cancer, bladder tumors, esophagus carcinomas, stomach cancer, rectal carcinomas, pancreas carcinomas, thyroid cancer, adrenal tumors, various types of leukemia and lymphomas, Hodgkin's disease, tumor illnesses of the CNS, soft-tissue sarcomas, bone sarcomas, benign and malignant mesotheliomas, especially intestine cancer, liver cancer, breast cancer, bronchial and lung carcinomas, melanomas, acute and chronic leukemias and benign papillomatosis tumors, by administering the very same compound.

The existence of working examples

Only one compound (SL 0101-1) was tested against human prostate and breast cancer cell lines (see pages 39-41 of the specification). Thus, the evidence in the examples is **not** commensurate in **scope** with the claimed invention and does not demonstrate criticality of a claimed range of the compounds of formula (III) and numerous and various cancers and also any Rsk specific inhibitor, in the claimed methods. See MPEP § 716.02(d).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

Further, unknown or future known tumors/cancers will require additional or future research to discover and diagnose. Therefore, the skilled artisan has to exercise **undue experimentation** to practice the instant invention.

Thus, the specification fails to provide sufficient support of the broad use of the compounds for treating numerous and various cancers recited in the instant claims and as a result, necessitating one of skill to perform an exhaustive search for the embodiments of compounds and cancers encompassed by the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factor and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test compounds and cancers encompassed in the instant claims, with no assurance of success.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21-24, 32 and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Matthes et al (Phytochemistry, 1980, 19, 2643-2650) in view of Bjorbaek et al (WO 00/66721), Marks et al (US 5,910,583), Kuijpers et al (US 5,733,523) of record and Pienta et al (Anticancer Research, 1994, 14, 2617-2620) newly cited.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Matthes et al disclose a compound of structural formula 7, wherein two of the three hydroxyl groups on the sugar moiety are acetylated (page 2645). This compound is structurally same as the compound claimed in instant claims 21-24 and 52. Matthes teaches that the extract

from the roots of Zingiber zerumbet (which contains compound 7 as an active agent) was tested against a rat neoplastic liver cell strain and found to be cytotoxic (page 2643, left column, Introduction, second and third paragraph). Even though Matthes teaches a compound that shows cytotoxicity towards neoplastic cells (cancer) and a composition comprising the same, he does not specifically teach that his compound is an Rsk inhibitor.

Bjoebaek et al teach inhibition of Rsk activity using nucleic acid construct expressing Rsk2 or a biologically active fragment thereof (page 2, line 26 through page 4, line 3; page 21, lines 1-7; example at pages 24 through 31). However, Bjorbaek does not teach a composition comprising the nucleic acid constructs as anticancer agents.

Kuijpers et al teach in general the use of antisense oligonucleotides and their pharmaceutical formulations for the treatment of tumors (see abstract, col. 1, lines 26-40) and Marks teaches in general a variety of uses for oligonucleotide formulations including treatment of tumors (col. 5, lines 9-25).

Based on the teachings of the prior art above one of ordinary skill in the art will recognize that:

1. Nucleic acid constructs can be used to inhibit Rsk activity and antisense-oligonucleotides have been used for treatment of cancer. Hence antisense-oligonucleotides and interfering oligonucleotides can be used for treating cancer by inhibiting Rsk activity.

2. Flavonoid glycoside of Mattes exhibit antineoplastic activity and like oligonucleotides can be used for inhibiting Rsk activity and hence inhibition of cell proliferation (cancer).

One of skill in the art would be motivated to use compounds of the type taught by Mattes since Pienta teaches that flavone compounds (compounds that are structurally similar to instant compound III) have anticancer properties (page 2617, left column, first two paragraphs).

Obviousness based on similarity of structure and function entails motivation to make and use the claimed compound in expectation that compounds similar in structure will have similar properties. Where prior art compound essentially brackets the claimed compounds and are well known anticancer/antitumor agents, one of ordinary skill in the art would be motivated to make the claimed compounds in searching for new anticancer/antitumor agents. In re Payne, 606 F. 2d 303, 203, USPQ, 245, 254-55 (C.C.P.A. 1979).

Claims 25-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bjorbaek et al (WO 00/66721) in view of Marks et al (US 5,910,583) and Kuijpers et al (US 5,733,523) of record.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Bjoebaek et al teach inhibition of Rsk activity using nucleic acid construct expressing Rsk2 or a biologically active fragment thereof (page 2, line 26 through page 4, line 3; page 21, lines 1-7; example at pages 24 through 31). The compounds of their invention can be used in the form of compositions (page 23, line 8 through page 24, line 20). However, Bjorbaek does not teach a composition comprising the nucleic acid constructs as anticancer agents.

Kuijpers et al teach in general the use of antisense oligonucleotides and their pharmaceutical formulations for the treatment of tumors (see abstract, col. 1, lines 26-40) and Marks teaches in general a variety of uses for oligonucleotide formulations including treatment of tumors (col. 2, lines 3-7; col. 5, lines 9-25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use antisense oligonucleotides and interfering oligonucleotides as Rsk specific inhibitors for the treatment of cancer since oligonucleotides have been used for the treatment of cancer and nucleic acid constructs are also known to inhibit Rsk activity.

One of ordinary skill in the art would be motivated to use the composition comprising an Rsk specific inhibitor in the method as instantly claimed since Rsk inhibition in addition to treating cancer also has other beneficial effects as taught by Bjoerbaek.

Response to Applicants Remarks

Applicants have presented arguments regarding the amendment of the instant claims for treatment of cancer and that the specification lends support for the treatment of breast and ovarian cancer and sarcoma. The said support is seen in the instant specification for the treatment of breast, ovarian cancer and sarcoma. The instant claims as explained above also encompass the treatment of cancer broadly for which enablement is not seen.

Conclusion

Claims 21-28, 32 and 51-53 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

GK

3/29/07

Shaojia Jiang
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Art Unit 1623